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EXAMINER	
RICCI, CRAIG D	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/555,343	KATO ET AL.	
	Examiner	Art Unit	
	CRAIG RICCI	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05/19/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-18, 21-23, 28-42* is/are pending in the application.

4a) Of the above claim(s) *16-18 and 21-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/19/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. The amendments filed 05/19/2009 were entered.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/19/2009 has been entered.

Response to Arguments

3. Applicants' arguments, filed 05/19/2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. **Claims 28-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Banker and Rhodes* (cited in a previous Action), *Fumihiro et al* (cited in a previous Action), *Hunik* (cited in a previous Action), *Makino et al* (cited in a previous Action), *Craig et al* (cited in a previous Action, and *Kim et al* (cited in a previous Action)**.

7. Instant claim 28 is drawn to a freeze-dried preparation comprising methylcobalamin and an excipient, wherein said excipient comprises at least one sugar (selected from glucose, fructose, maltose, lactose, sucrose and trehalose) in an amorphous state. More specifically, the amorphous sugar is present in an amount of at least 20% by weight, based on the total weight of the excipient (instant claim 29).

8. As discussed in the previous Action, "[m]any drugs are too unstable – either physically or chemically – in an aqueous medium to allow formulation as a solution, suspension, or emulsion. Instead, the drug is formulated as a dry powder" (*Banker and Rhodes*, Page 394, Column 2). It is generally known that vitamins, including vitamin B_{12}, (of which methylcobalamin is the active form) are not very stable and that degradation is observed on storage. Specifically, *Hunik* discloses that "methylcobalamin… [is] known to be unstable to light in isolated form and [is] easily transformed to hydroxycobalamin in aqueous solution" (Page 1, Lines 23-26). Conversely, *Fumihiro et al* teach stable freeze-dried preparations comprising vitamin B_{12}

(Abstract). Accordingly, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to formulate methylcobalamin as a freeze-dried preparation. The skilled artisan, recognizing the instability of methycobalamin (as taught by *Hunik*) would have been motivated to formulate methylcobalamin as a dry powder (as taught by *Banker and Rhodes*), specifically by freeze-drying (as taught by *Fumihiro et al*). In view of *Fumihiro et al*, which teach stable freeze-dried preparations comprising vitamin B_{12} (and considering that methylcobalamin is the active form of vitamin B_{12}), the skilled artisan would have reasonably predicted that a freeze-dried preparation comprising methylcobalamin would possess enhanced stability and thus overcome the problems disclosed by *Hunik*.

9. Furthermore, in formulating the freeze-dried preparation comprising methylcobalamin for the reasons discussed above, the skilled artisan would have found it *prima facie* obvious to include one or more excipients wherein said excipient(s) comprises at least one sugar (selected from glucose, fructose, maltose, lactose, sucrose and trehalose) in an amorphous state as recited by instant claim 28 for the following reasons:

10. **FIRST**, the inclusion of excipients - wherein said excipient comprises at least one sugar - as cryoprotectants during freeze-drying is well known in the art. Specifically, as disclosed by *Craig et al*, "cryoprotectants are materials which are commonly added during the freeze drying process in order to afford protection of the drug from degradation… The most commonly used cryoprotectants are sugars, although polymers and amino acids may also be used" (Page 202, Columns 1-2). Similarly, *Makino et al* (US 4,948,788) teach a freeze-dried preparation comprising vitamin D_3 (which, like methylcobalamin, is a vitamin that is unstable to light (Column 1, Lines 23-24)) and an excipient (Abstract) having good stability (Column 2, Line 8)

wherein the "excipients usable in the present invention may include amino acids, monosaccharides, disaccharides..." [and] "[m]onosaccharides and disaccharides may include mannitol… lactose… and the like" (Column 2, Lines 35-39). Thus, as stated in the previous Action, in view of *Craig et al*, the skilled artisan would have found it obvious to include excipients, such as sugars, in formulating the freeze-dried preparation comprising methylcobalamin with the reasonable expectation that their inclusion would protect the methylcobalamin from the possibility of degrading during freezing. More specifically, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to include, as the excipient, mannitol and lactose (or the like) in view of *Makino et al* which teach that the recited excipients are known excipients useable in stable freeze-dried preparations comprising light-unstable vitamins. Accordingly, the skilled artisan would have included mannitol and lactose (or the like) in the recognition that degradation of any drug is a concern during freeze-drying and that sugars are well known excipients useful as cyroprotectants during freeze-drying the drug preparations in order to overcome this defect (in view of *Craig et al*) and, furthermore, in the recognition that mannitol, lactose and the like are specifically known as usable excipients in freeze-dried preparations comprising vitamins (in view of *Makino et al*). Thus, the person of ordinary skill in the art would have reasonably predicted that the inclusion of mannitol and lactose (or the like) would successfully provide cryoprotection during freeze-drying of a vitamin, such as methylcobalamin. As stated by the Court in *KSR International Co., v. Teleflex Inc.*, 82 USPQ2d 1385 (2007) "when a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious" quoting *Sakraida v. AG Pro, Inc.*,

189 USPQ 449 (1976). In the instant case, the recited excipients are known in the art as cryoprotectants in freeze-dried preprations, including freeze-dried vitamin preparations. As such, the arrangement of old excipients with each performing the same function of cryoprotection that they had been known to perform and yielding no more than one would expect from such an arrangement, is *prima facie* obvious. That is, the skilled artisan would have found it *prima facie* obvious to combine known prior art elements according to known methods to yield predictable results.

11. And **SECOND**, as noted by *Banker and Rhodes*, mannitol is a common excipient in freeze-dried preparations, but "crystallization of mannitol during heating is believed to be the underlying cause of vial breakage in mannitol-based formulations" (Page 399, Column 1). Although *Banker and Rhodes* are discussing freeze-dried preparations comprising proteins, the skilled artisan would similarly wish to avoid vial breakage while formulating mannitol-based vitamin formulations. Accordingly, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made use **amorphous** excipients in order to avoid crystallization and thus reduce the likelihood of vial breakage during the freeze-drying process. In order to achieve this, the skilled artisan would turn to *Kim et al* which teach that freeze-dried preparations comprising mannitol **and** a cosolute such as sucrose or lactose provide an amorphous excipient (entire document). More specifically, *Kim et al* report that "the relative concentration threshold above which crystalline mannitol is detected by X-ray diffraction is about 30% (w/w)" and that that "the glass transition decreases markedly as the relative concentration of mannitol increases" (Page 933, Column 2). Accordingly, in order to avoid vial breakage, the skilled artisan would have found it *prima facie* obvious to include mannitol and a

cosolute such as sucrose or lactose. Furthermore, since *Kim et al* disclose that "the relative concentration threshold above which crystalline mannitol is detected by X-ray diffraction is about 30% (w/w)" (Page 933, Column 2), the skilled artisan would have found it *prima facie* obvious to include at least 70% sucrose or lactose (w/w) in the excipient (see also *Kim et al*, Page 934, Table I). The skilled artisan would have been motivated to include sucrose or lactose in an amount that is at least 20% by weight (as recited by the instant claim), more specifically at least 70% by weight, in order to maintain mannitol in an amorphous state and thus avoid or reduce the likelihood of vial breakage.

12. Accordingly, in view of all of the foregoing, it would have been *prima facie* obvious to formulate methylcobalamin as a freeze-dried preparation in order to enhance its stability. In doing so, it would have also been *prima facie* obvious to include as an excipient, a cryoprotectant comprising mannitol and lactose to protect the methylcobalamin from the possibility of degrading during the freezing process. More specifically, it would have been obvious to include a cryoprotectant comprising at least 20% by weight **amorphous** lactose in order to avoid crystallization of mannitol during the process and thus reduce the likelihood of vial breakage during freeze-drying. As such, instant claims 28-29 are rejected as *prima facie* obvious.

13. Applicants traverse on a variety of grounds:

14. First, Applicants note that the prior art references discussed in the previous Action and reiterated above are deficient in that: (A) *Banker and Rhodes* do not address methycobalamin instability in freeze-dried preparations; (B) *Fumihiro* and *Hunik* are both silent as to how to solve the problem of storage instability of methylcobalamin in a lyophilized preparation; (C) *Craig* and *Kim* and *Makino* are all silent as to the use of the amorphous excipient, including sugar, for

stabilization of the freeze-dried preparation comprising methylcobalamin;, etc. Each of the arguments has been fully considered but are not considered persuasive since, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091 (Fed. Cir. 1986).

15. Second, Applicants argue that "[t]he problem facing the inventors was not stabilizing the preparation ***during*** the lyophilization, but rather, the long-term stability of preparations that contain methylcobalamin" (Applicant Argument, Page 10, emphasis added). As such, Applicants seem to implicitly acknowledge that it would have been obvious to formulate the preparation as recited by instant claims 28-29 to stabilize the preparation ***during*** the lyophilization for the reasons discussed above. Nevertheless, as argued by Applicants, "the question is not whether the artisan would have been motivated to formulate methycobalamin as a freeze-dried powder. Instead, the problem was that the long-term stability of preparations of pure methylcobalamin was not good when the methylcobalamin was stored as a freeze-dried powder" (Applicant Argument, Page 11). Or, in other words, "Applicants are concerned with the storage stability of methylcobalamin, not with the stability during freeze-drying" (Applicant Argument, Page 15). However, it is not necessary that the prior art suggest the combination to achieve the ***same*** advantage or result discovered by Applicant. See *In re Kahn*, 441 F.3d 997 (Fed. Cir. 2006). In the instant case, as discussed above, the skilled artisan would have been motivated to formulate the instantly recited preparation in order to provide a stable formulation that is not subjected to extensive degradation and does not result in vial breakage ***during*** the

lyophilization. The fact that Applicant was not concerned with stability or vial breakage during freeze-drying, and has recognized another advantage (namely, long-term stability on storage) which would flow naturally from the above suggestion of the prior art cannot be the basis for patentability when the differences would otherwise by obvious. See *Ex pare Obiaya*, 227 USPQ 58 (BPAI 1985).

16. Third, Applicants argue that certain references teach away from the combination. In particular, Applicants contend that *Banker and Rhodes* state a preference for crystallization over amorphous states and specifically note that some solutes (such as mannitol) may form a metastable amorphous phase initially on freezing and then crystallize when material is heated, but can be induced to crystallize via thermal treatment, for example (Applicant Argument, Page 11). While it is agreed that *Banker and Rhodes* state that "[i]n general, crystallization of the solute is desirable in terms of freeze-drying properties" (Page 399, Column 2), they also note that "[w]hile crystallinity of a drug is generally desirable for freeze-drying, ***it is often important for excipients to remain amorphous***" (Page 400, Column 1, emphasis added). Accordingly, Applicants' argument that *Banker and Rhodes* teach away from using an amorphous excipient is not found persuasive. Applicants, however, additionally argue that the disclosure of *Banker and Rhodes* - which is specific for protein stabilization - fails to provide any chemical nexus between protein stabilization and stabilization of a methylcobalamin compound (Applicant Argument, Page 12). Yet, the skilled artisan would have predicted with a high expectation of success that addition of a cryoprotectant as taught by *Banker and Rhodes* would function to stabilize either proteins ***or*** vitamins.

17. Applicant also argues that *Banker and Rhodes* teach away "from the use of a disaccharide such as maltose and lactose, by stating that they should be approached with caution" (Applicant Argument, Page 12). More specifically, *Banker and Rhodes* state that "[d]isaccharides, such as sucrose and trehalose, are, in general, the most effective protectants [and] [t]he use of maltose and lactose, also disaccharides, should be approached with caution, since they are both reducing sugars" (Page 400, Column 1). While it is acknowledged that *Banker and Rhodes* teach a preference for sucrose and trehalose, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed" *In re Fulton*, 391 F.3d 1201 (Fed. Cir. 2004).

18. Finally, Applicants argue that *Craig et al* also teach away by noting that "[g]iven the potential advantages of preparing drugs in an amorphous form, the question arises as to why this approach is not used more often. The single most important reason is undoubtedly the problems associated with stability, both physical and chemical" (Page 193, Column 2). However, *Craig et al* also point out that, while "[t]he amorphous state is, by definition, metastable with regard to the crystalline material [and] hence amorphous drugs will tend to revert to crystalline form over a period of time… with some knowledge of the fundamental physico-chemical properties of the drug in question it is possible to make some assessment of the likelihood of devitrification and to recommend storage conditions which will minimize the risk of the process occurring" (Page 194, Column 1). Thus it is clear that the skilled artisan, having "some knowledge of the fundamental physico-chemical properties of the drug in question" would be able to minimize the risks associated with preparing drugs in an amorphous form. Furthermore, as stated in the previous

Action, the teaching that the amorphous state may reduce chemical and physical stability of the preparation would not dissuade the skilled artisan in view of *Craig et al* which specifically state that "the onset of the devitrification process may be so slow so as to be effectively irrelevant within the storage time of a product" (Page 180, Column 1). As such, it is not found persuasive that *Craig et al* teach away from the instant invention.

19. Instant claims 30-32 are drawn to the preparation of claim 1 further comprising a pH adjuster (claim 30) and/or an antioxidant (claims 31 and 32). *Makino et al*, which is drawn to a stabilized freeze-dried preparation comprising vitamin D_3 (which, like methylcobalamin, is a vitamin that is unstable to light in aqueous compositions) and an excipient, teach the inclusion of antioxidants and buffering agents (Column 3, Lines 20-31) in the preparation. Accordingly, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to further include a pH adjuster and an antioxidant because, in view of *Makino et al* and in view of *KSR International Co. v. Teleflex, Inc* as discussed above, the arrangement of old ingredients (antioxidants and pH buffers) with each performing the same function of enhancing stabilization that they had been known to perform and yielding no more than one would expect from such an arrangement, is *prima facie* obvious. That is, the skilled artisan would have found it *prima facie* obvious to combine known prior art elements according to known methods to yield predictable results.

20. **Claims 33-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Banker and Rhodes* (cited in a previous Action), *Fumihiro et al* (cited in a previous Action), *Hunik* (cited in a previous Action), *Makino et al* (cited in a previous Action), *Craig et al* (cited in a previous Action, and *Kim et al* (cited in a previous Action) as applied to instant claims 28-**

29 above in further view of *FDA Guide to Inspections of Lyophilization of Parenterals* (cited in a previous Action).

21. Instant claim 33 is drawn to the freeze-dried preparation of claim 28 wherein the methylcobalamin is also in an amorphous state. The *FDA Guide to Inspections of Lyophilization of Parenterals* states that one problem associated with lyophilized powders is poor solubility, "[i]ncreased time for reconstitution at the user stage may result in partial loss of potency if the drug is not completely dissolved, since it is common to use in-liner filters during administration to the patient" (Page 14, Paragraph 2). As taught by *Craig et al*, amorphous drugs possess enhanced dissolution profiles compared to crystallized drugs (Page 191). Accordingly it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to include methylcobalamin in an amorphous state. The skilled artisan would have been motivated to do so in order to ensure adequate dissolution and thus overcome the problem associated with lyophilized drugs taught by the *FDA Guide*. Furthermore, the teaching that the amorphous state may reduce chemical and physical stability of the preparation would not dissuade the skilled artisan in view of *Craig et al* which specifically state that "the onset of the devitrification process may be so slow so as to be effectively irrelevant within the storage time of a product" (Page 180, Column 1).

22. Applicants argue, however, that the FDA report teaches away from the instant invention by stating that "[m]anufacturers should be aware of the stability of lyophilized products which exhibit partial or complete meltback. Literature shows that for ***some*** products, such as cephalosporins, that the crystalline form is more stable than the amorphous form of lyophilized product. The amorphous form may exist in the 'meltback' portion of the cake where there is

incomplete sublimation". Although Applicants do **not** assert that amorphous methylcobalamin behaves like cephalosporins, *assuming arguendo* that the amorphous form of methylcobalamin might similarly exist in the 'meltback' portion of the cake, the skilled artisan would not be dissuaded from formulating the preparation as discussed above since the person of ordinary skill in the art would "be aware of the stability of lyophilized products which exhibit partial or complete meltback" and, as disclosed by the FDA repot, would carry out "good pharmaceutical practice to perform 100% inspection of parental produts. This includes sterile lyophilized powders. Critical aspects would include the presence of correct volume of cake and the cake appearance" (FDA report, First Paragraph under FINISHED PRODUCT INSPECTION).

23. Instant claim 34, which depends from claim 33 and specifies the amount of excipient present is at least 20% by weight is rejected for the same reasons as discussed above as to instant claim 29.

24. Instant claims 35 and 36 are drawn to the preparation of claims 33 or 34 further comprising a pH adjuster (claim 35) and/or an antioxidant (claims 36). *Makino et al*, which is drawn to a stabilized freeze-dried preparation comprising vitamin D_3 (which, like methylcobalamin, is a vitamin that is unstable to light in aqueous compositions) and an excipient, teach the inclusion of antioxidants and buffering agents (Column 3, Lines 20-31) in the preparation. Accordingly, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to further include a pH adjuster and an antioxidant because, in view of *Makino et al* and in view of *KSR International Co. v. Teleflex, Inc* as discussed above, the arrangement of old ingredients (antioxidants and pH buffers) with each performing the same function of enhancing stabilization that they had been known to perform

and yielding no more than one would expect from such an arrangement, is *prima facie* obvious. That is, the skilled artisan would have found it *prima facie* obvious to combine known prior art elements according to known methods to yield predictable results.

25. Instant claims 37-42 are drawn to are all drawn to a freeze dried preparation comprising methylcobalamin and an excipient wherein the freeze dried preparation is obtained by a specific process. As stated by MPEP 2113:

> **PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY THE STEPS**
>
> "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted)

. In the instant case, the instantly claimed product in the product-by-process claim is obvious from a product of the prior art as previously discussed in view of *Banker and Rhodes*, *Fumihiro et al*, *Hunik*, *Makino et al*, *Nail et al*, *Kim et al*, *FDA Guide to Inspections of Lyophilization of Parenterals*, and *Craig et al*. Accordingly, the obvious product as obtained by the process recited by claims 37-42 is rejected as *prima facie* obvious in view of *In re Thorpe*.

26. **Instant claims 28-30, 37-38 and 41 are rejected rejected under 35 U.S.C. 103(a) as being unpatentable over *Takatoshi et al* (JP 63-313736; Abstract only – awaiting a certified translation of the full document)**.

27. As discussed above, instant claims 28-29 are drawn to a freeze-dried preparation comprising methylcobalamin and an excipient, wherein said excipient comprises at least one sugar (selected from glucose, fructose, maltose, lactose, sucrose and trehalose) in an amorphous state. More specifically, the amorphous sugar is present in an amount of at least 20% by weight, based on the total weight of the excipient. Additionally, as recited by instant claim 30, the freeze-dried preparation further comprises a pH adjuster.

28. *Takatoshi et al* discloses a freeze-dried vitamin complex preparation comprising 20-70% of an excipient such as, for example, lactose, and a vitamin wherein the pH of the solution is adjusted and freeze-dried (Abstract). Notably, as evidenced by the attached synopsis of *Takatoshi et al* provided as DERWENT Accession Number 1989-042241, the vitamins include vitamin B_{12}. As such, the specific combination of features claimed is disclosed within a broad generic ranges taught by the reference. However, such "picking and choosing" within several variables does not *necessarily* give rise to anticipation. *Corning Glass Works v. Sumitomo Elec.,* 868 F.2d 1251, 1262 (Fed. Circ. 1989). Where, as here, the Abstract does not provide any motivation to select this specific combination of variables, anticipation cannot be found. That being said, however, it must be remembered that "[w]hen a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious". *KSR v. Teleflex*, 127 S,Ct. 1727, 1740 (2007) (quoting *Sakraida v. A.G. Pro*, 425 U.S. 273, 282 (1976)). "[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious", the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." Addressing the issue of obviousness, the

Supreme Court noted that the analysis under 35 USC 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR v. Teleflex*. The Court emphasized that "[a] person of ordinary skill is… a person of ordinary creativity, not an automaton." Consistent with this reasoning, it would have obvious to have selected various combinations of various disclosed ingredients (namely, vitamin B_{12} and lactose) from within a prior art disclosure, to arrive compositions "yielding no more than one would expect from such an arrangement". Furthermore, it is asserted that lactose (i.e., the excipient in the freeze-dried formulation) would necessarily exist at least partially in an amorphous state. As stated in *In re Best, Bolton, and Shaw*, "Where… the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product" 195 USPQ 430, 433, 562 F2d 1252 (CCPA 1977). In the instant case, the claimed and prior art formulations are substantially similar. Accordingly, it is asserted that, absent evidence to the contrary, the lactose would exist in an amorphous state. See also *In re Fitzgerald* 205 USPQ 594, 597, 619 F2d 67 (CCPA 1980): the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on."

29. Instant claims 37-38 and 41 are all drawn to a freeze dried preparation comprising methylcobalamin and an excipient wherein the freeze dried preparation is obtained by a specific

PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY THE STEPS

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted)

process. As stated by MPEP 2113: . In the instant case, the instantly claimed product in the product-by-process claim is obvious from a product of the prior art as previously discussed in view of *Takatoshi et al*. Accordingly, the obvious product as obtained by the process recited by claims 37-38 and 41 is rejected as *prima facie* obvious in view of *In re Thorpe*.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571) 270-5864. The examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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